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DNA-supported palladium nanoparticles as a reusable catalyst for the copper- and ligand-free Sonogashira reaction

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DNA nanotechnology has recently emerged as a powerful discipline with diverse applications. However, studies focused on the combination of DNA and metal nanoparticles for catalyst design are scanty. We have prepared a catalyst composed of palladium nanoparticles supported on DNA which has been characterised by TEM, SEM, EDX, UV, FTIR and XPS. The catalyst, mainly composed of Pd(II) and Pd(IV) species in the form of oxides, has been effectual in the copper- and ligand-free Sonogashira-Hagihara coupling of aryl iodides with terminal aromatic and aliphatic alkynes. The products are obtained in 54–86% isolated yields using low catalyst loading (0.5 mol%) under mild conditions (65 °C) in methanol without air exclusion. Moreover, the catalyst can be easily recovered and reused in five cycles and shows better performance than an array of commercial palladium catalysts. The mechanistic aspects of the reaction are also tackled in detail.

Introduction

Nowadays, it is indisputable that the inertia that accompanies discoveries in nanoscale sciences and technology is a car race without brakes. In this context, nanoparticles (NPs)¹ are among the most attractive nanomaterials due to their dependence on properties associated with its size,² playing a prominent role in pharmacology as an alternative to drug delivery, in nanoelectronic systems as sensors and in chemistry as a catalysts.³ On the other hand, enzymes, lipids and nucleic acids are advantageous biomaterials because they are non-toxic, environmentally friendly, readily available and biodegradable; that is why the successful preparation of bio-nanoparticles such as DNA-NPs has recently emerged.⁴ Leaving aside the relevance of the genetic information inherent to DNA, nucleic acids have also become useful as chemical and physical tools. Indeed, the combination of the physical and chemical properties of DNA with nanotechnology has given rise to DNA nanotechnology, a discipline covering the design and study of synthetic structures based on DNA and its manifold applications.⁵ The high affinity of DNA for transition metals makes it suitable to act as a ligand for the metallization of DNA, as a template for the synthesis of metal nanomaterials and as a support for metal nanoparticles.⁶ In spite of the soaring upsurge of interest in developing DNA-metal nanoparticle hybrid materials, their application in heterogeneous catalysis is still in its infancy.⁶ For instance, in such a highly productive research area in catalysis as the carbon-carbon coupling,⁷ to the best of our knowledge, there are only three related reports, dealing with the application of PdNPs-DNA to the Suzuki-Miyaura cross-coupling reaction.⁸

In recent decades, acetylene chemistry has experienced a renaissance due not only to its exploitation in the chemical industry, biochemistry and materials science, but also because of its versatility for the synthesis of natural products and pharmaceuticals of interest.⁹ Alkyne chemistry has been mainly driven by the progress of new synthetic methodologies based on transition-metal catalysis, where palladium always occupies a leading position. In this scenario, the Sonogashira-Hagihara reaction is currently one of the most widely practiced methods to prepare alkyl and aryl acetylenes as well as conjugated enynes.¹⁰

The standard Sonogashira catalytic system involves a palladium source in the presence of copper(I) and an amine. Depending on whether the catalyst is homogeneous or heterogeneous, its nature (salt, complex, supported metal, nanoparticles, etc.) and the presence or absence of copper (and its oxidation state) and amine, other agents also come into play; such is the case of ligands (e.g., PPh₃) or promoters/stabilisers (e.g., tetra-*n*-butylammonium halides). However, both from the practical and environmental point of view, simpler catalytic systems which function under mild conditions in the absence of copper, amines and the aforesaid additives are desirable. In this vein, the development of air-stable and recyclable catalysts should be also a priority.

The solvent issue is another matter of concern, as most of the common solvents deployed for this coupling reaction are not recommended; they have been ranked according to a set of safety, health and environment criteria as follows: toluene and acetonitrile (problematic), 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidin-2-one (hazardous).¹¹

Therefore, despite the vast research devoted to the title reaction, the design and implementation of new catalysts with upgraded properties which operate under sustainable conditions is welcome.

To the best of our knowledge, hybrid bio-metallic catalysts based on Pd/DNA have not been applied to the Sonogashira-Hagihara reaction hitherto. Due to our ongoing interest in metal nanoparticles¹² and transition-metal catalysed carbon-carbon coupling reactions,¹³ we want to present herein our effort to devise a catalyst composed of PdNPs on DNA for the

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efficient copper-, amine- and ligand-free Sonogashira-Hagihara reaction of aryl iodides and terminal alkynes; we have also made every endeavour to understand its mode of action.

Results and discussion

Catalyst preparation and characterisation

The catalyst was prepared following a simple procedure in the absence of any stabilising or nucleation agent, i.e., by mixing Li_2PdCl_4 , NaOAc and salmon-sperm DNA in methanol at room temperature with stirring for 48–72 hours (Figure 1).

The resulting brown solid was characterised by different means. The palladium content in the catalyst, 6.4 wt%, was determined by inductively coupled plasma optical emission spectroscopy (ICP-OES). Analysis by Transmission Electron Microscopy (TEM) (Figure 2, top) revealed the presence of near spherical nanoparticles of $ca. 7.1 \pm 3.5$ nm (Figure 3), uniformly distributed on the DNA surface with no sign of agglomeration. Scanning Electron Microscopy (SEM) brought into view morphological and topological information of the surface as visualised in Figure 2 (bottom), which corroborated this regular particle dispersion.



DNA, Li_2PdCl_4 and NaOAc in MeOH

Fig. 1 Preparation sequence of PdNPs/DNA.

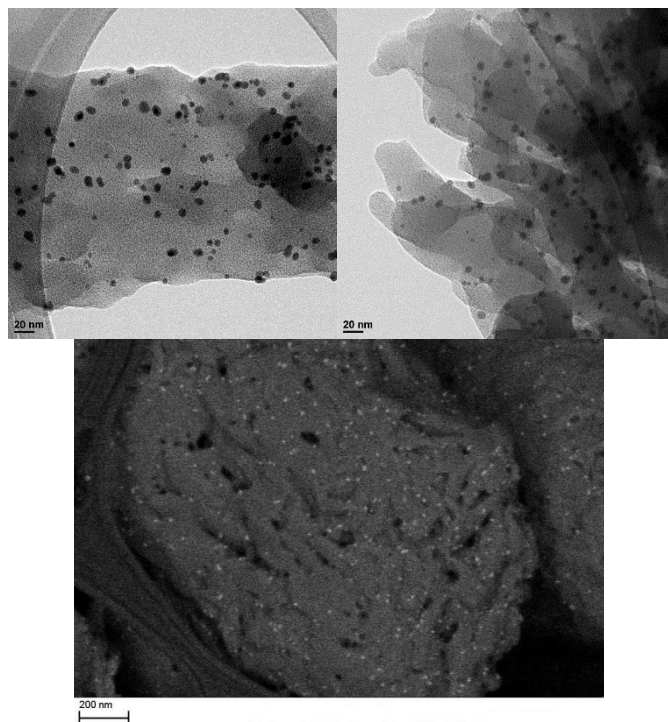


Fig. 2 TEM (top) and SEM (bottom) images of PdNPs/DNA.

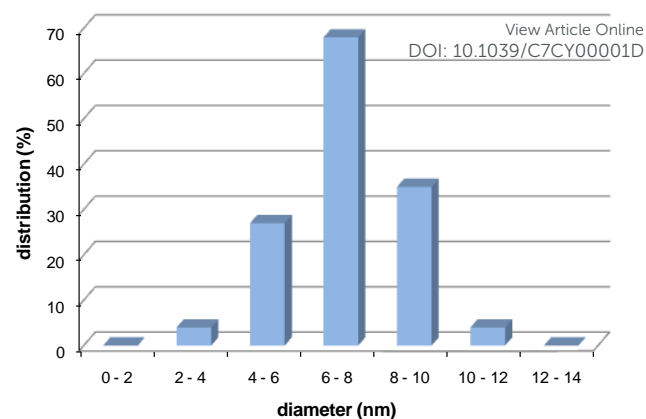


Fig. 3 Particle size distribution of PdNPs/DNA. The sizes were determined for 138 nanoparticles selected at random.

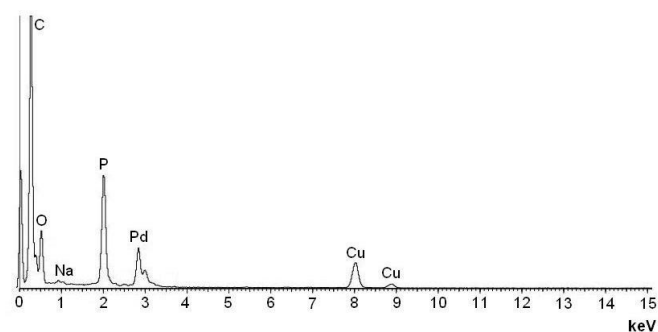


Fig. 4 EDX spectrum of PdNPs/DNA run on a copper grid.

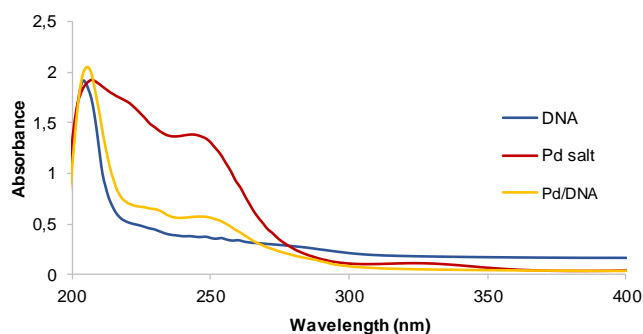


Fig. 5 UV spectrum of DNA, Li_2PdCl_4 and PdNPs/DNA in ethanol.

Energy-dispersive X-ray (EDX) analysis on various regions confirmed the presence of palladium, with energy bands around 3 eV corresponding to the Pd L lines,¹⁴ as well as that of the elements present in DNA, with the following atomic percentage: 73.6% carbon, 10.8% oxygen, 12.1% P, 0.35% Na and 3.2% Pd (Figure 4). The nitrogen content in the catalyst, as determined by elemental analysis, was found to be 15% (14% for DNA). UV comparative absorption spectra of DNA (206 nm), Li_2PdCl_4 (207 and 243 nm) and PdNPs/DNA (206 and 251 nm) in ethanol showed the composite character of the latter (Figure 5). The fact that no resonant peak appeared above 300 nm was in agreement with the PdNPs mostly being <10 nm in size.¹⁵ The most meaningful bands observed by IR spectroscopic analysis of PdNPs/DNA come into view at 3000–3500 cm^{-1} (N-H and O-H stretching), 1640, 1570 and 1540 cm^{-1} (C=O, C=N, C=C stretching and N-H bending of the

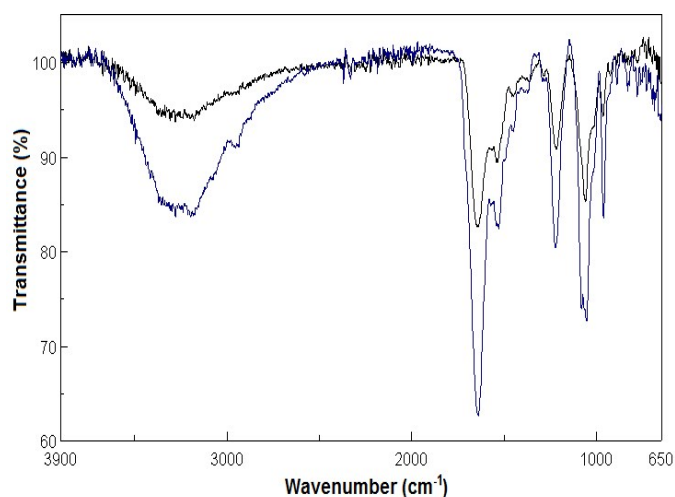


Fig. 6 FT-IR spectrum of DNA (blue) and PdNPs/DNA (black).

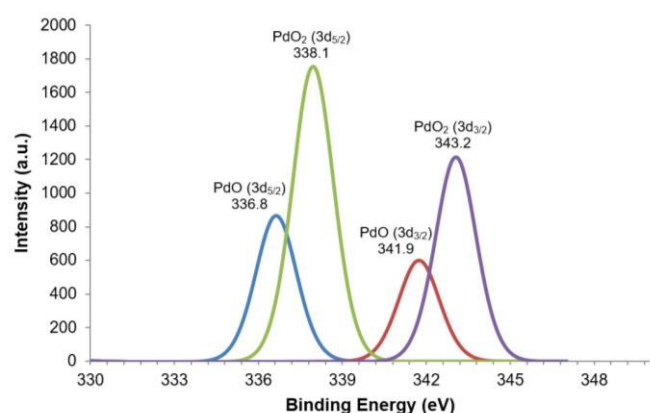


Fig. 7 XPS spectrum of PdNPs/DNA at the Pd 3d_{5/2} and Pd 3d_{3/2} levels.

nucleobases), 1217 cm⁻¹ (asymmetric PO₂⁻ stretching), 1062 and 965 cm⁻¹ (symmetric PO₂⁻ and P–O–C backbone stretching) (Figure 6).¹⁶ The IR spectra of DNA and PdNPs/DNA look alike, with the only appreciable difference being that the peak at 1062 cm⁻¹ in PdNPs/DNA is resolved into two peaks (1078 and 1051 cm⁻¹) in the parent DNA.

XPS analysis showed two deconvoluted Pd (3d_{5/2}) peaks at 336.8 and 338.1 eV, and two deconvoluted Pd (3d_{3/2}) peaks at 341.9 and 343.2 eV (Figure 7). In principle, the presence of Pd(0) can be practically ruled out as the expected binding energies (335.3 and 340.5 eV)¹⁷ are distinctly lower than those displayed in Figure 7. The peaks at 336.8 and 341.9 eV could be assigned to Pd(II) in the form of PdO,¹⁸ whereas those at 338.1 and 343.2 eV are very close to those in K₂PdCl₄.¹⁹ Although it may well be true that some Li₂PdCl₄ was present on the support, it is important not to overlook the fact that neither Cl nor Li were detected by EDX. On the other hand, these binding energies are akin to those reported for Pd(IV) in the form of PdO₂.²⁰ Therefore, it can be concluded that PdNPs/DNA is primarily composed of Pd(II) and Pd(IV) species in the form of the corresponding oxides (PdO and PdO₂, respectively). These results differ from those found for DNA-modified graphene/PdNPs,^{8b} oligonucleotide stabilised PdNPs^{8c} and DNA-templated Pd nanowires,^{16b} where the use of

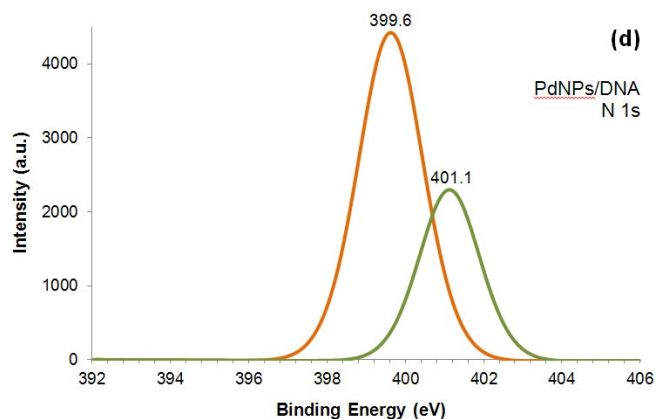
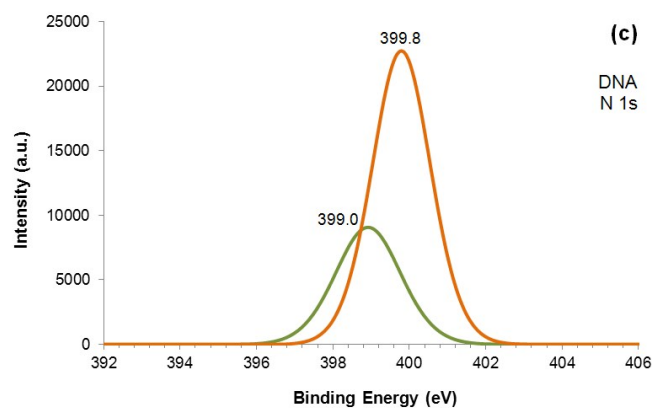
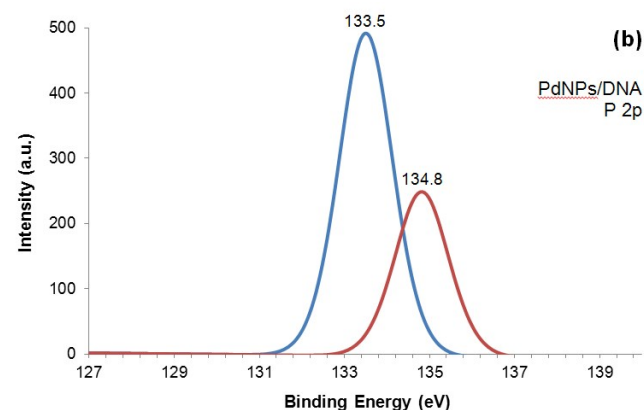
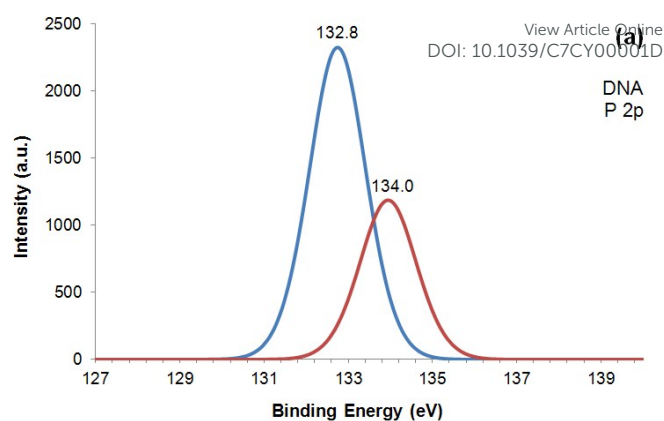


Fig. 8 XPS spectra of DNA [(a), (c)] and PdNPs/DNA [(b), (d)] at the P 2p and N 1s levels.

a reductant (e.g., NaBH_4) favoured the substantial formation of Pd (0).

XPS was found to be a useful tool also to analyse the N and P content as well as the interplay of these atoms with their chemical environment. For instance, the relative atomic percentage in surface allowed to estimate the N/P ratio, which did not practically vary from DNA (8.03) to PdNPs/DNA (8.77); this ratio was notably higher than that published for the commercial nucleotides (2.0–4.0).²¹ XPS spectra at the P 2p and N 1s levels were carefully examined, with the following results (Figure 8): (a) the DNA peaks at 132.8 (P 2p_{3/2}) and 134.0 eV (P 2p_{1/2}) are in agreement with the presence of phosphate units (Figure 8a);²² (b) the area ratio between these two peaks remains unaltered from DNA to PdNPs/DNA (2.0 vs. 2.1, respectively) but they are shifted, to the same extent, to higher binding energy in the latter case [133.5 (P 2p_{3/2}) and 134.8 eV (P 2p_{1/2})] (Figure 8b); this shift points to the existence of some phosphate-PdNPs interaction; (c) the DNA peaks at 399.0 and 399.8 eV (N 1s) can be correlated with the imino (N=C) and amino-type (N-H) bonds of the nucleobases, respectively (Figure 8c);²³ (d) the N 1s area ratio in DNA is very similar to that in PdNPs/DNA (2.2 and 2.0, respectively); (e) the most important feature is, however, that the N 1s amino peak in PdNPs/DNA maintains nearly the same binding energy (399.6 eV) while the N 1s imino peak has been significantly shifted to higher binding energy (401.1 eV) (Figure 8d).

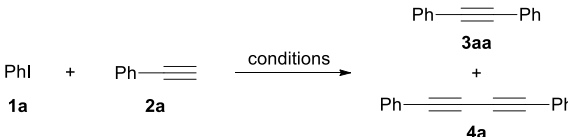
The affinity of DNA for transition metals has been generally simplified to adsorption studies of the individual pyrimidine and purine bases on zero-valent copper,^{24a-c} silver and gold^{24d} surfaces. DFT calculations on a $(\text{C}_3\text{TA}_2)_3\text{C}_3\text{T}$ DNA motif disclosed that the preferential binding site for a Pd atom was the N3 of the cytosines (i.e., the imino N).²⁵ However, to the best of our knowledge, the modes of interaction of DNA with (oxidised) palladium nanoparticles have not been identified so far. The results of our XPS study suggest that the PdNPs are stabilised on DNA through a primary interaction with the imino N of the nucleobases and a secondary interaction with the phosphate units, both located in the periphery of the double-stranded

helix (Figure 9); the amino functionalities seem unaffected in this sense, taking part in the bases intermolecular hydrogen bonding.²⁶

Optimisation of the reaction conditions

The cross coupling of iodobenzene (**1a**) and phenylacetylene (**2a**) was chosen as a model reaction in order to optimise the catalytic system and reaction conditions (Table 1); all reactions were performed at 65 °C (optimised temperature) in air. A first approach involving 0.5 mol% Pd, the standard co-catalysis by CuI and Cs_2CO_3 as the base gave moderate conversions into **3aa** only in dioxane and MeOH:H₂O (1:1), together with considerable amounts of the diyne **4a** derived from alkyne homocoupling²⁷ (Table 1, entries 1–6). A remarkable improvement was noticed in the absence of CuI, particularly, when using polar protic organic solvents (Table 1, entries 7–12); MeOH was shown to be the best one, leading to a quantitative conversion into **3aa** with no detectable diyne (Table 1, entry 10).

Table 1 The Sonogashira reaction of iodobenzene (**1a**) and phenylacetylene (**2a**).^a

					
Entry	Pd/CuI (mol%)	Solvent	Base	Time (h)	3aa/4a (%) ^b
1	0.50/5	dioxane	Cs_2CO_3	24	54/68
2	0.50/5	DMSO	Cs_2CO_3	24	-/-
3	0.50/5	EtOH	Cs_2CO_3	24	-/56
4	0.50/5	MeOH	Cs_2CO_3	24	8/31
5	0.50/5	MeOH:H ₂ O (1:1)	Cs_2CO_3	24	51/33
6	0.50/5	H ₂ O	Cs_2CO_3	24	-/-
7	0.50/-	dioxane	Cs_2CO_3	24	3/-
8	0.50/-	DMSO	Cs_2CO_3	24	-/-
9	0.50/-	EtOH	Cs_2CO_3	24	71/15
10	0.50/-	MeOH	Cs_2CO_3	24	>99/-
11	0.50/-	MeOH:H ₂ O (1:1)	Cs_2CO_3	24	78/-
12	0.50/-	H ₂ O	Cs_2CO_3	24	9/2
13	0.50/-	MeOH	Na_2CO_3	24	27/-
14	0.50/-	MeOH	K_2CO_3	24	29/-
15	0.50/-	MeOH	Et_2NH	24	12/-
16	0.50/-	MeOH	$i\text{Pr}_2\text{NH}$	24	11/1
17	0.50/-	MeOH	Et_3N	24	14/-
18	0.50/-	MeOH	-	24	-/-
19	0.13/-	MeOH	Cs_2CO_3	24	11/-
20	0.25/-	MeOH	Cs_2CO_3	24	30/-
21	0.75/-	MeOH	Cs_2CO_3	24	87/-
22	0.50/-	MeOH	Cs_2CO_3	2	53/-
23	0.50/-	MeOH	Cs_2CO_3	4	79/-
24	0.50/-	MeOH	Cs_2CO_3	7	84/-
25	0.50/-	MeOH	Cs_2CO_3	10	85/-

^a Iodobenzene (**1a**, 0.24 mmol), phenylacetylene (**2a**, 0.24 mmol) and PdNPs/DNA (2 mg), base (0.3 mmol), solvent (1 mL) at 65 °C in air. ^b Conversion determined by GLC using *n*-decane as the internal standard referred to **1a**.

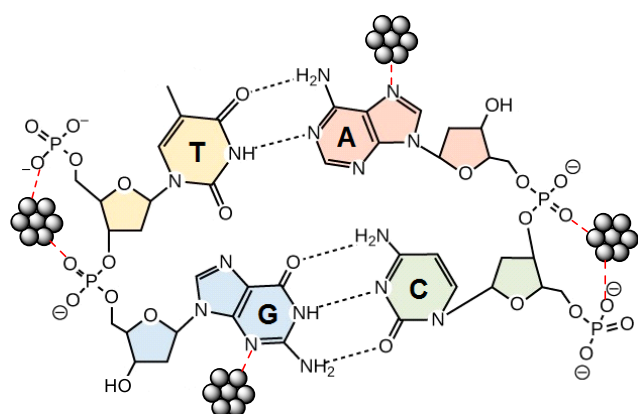


Fig. 9 Model showing the estimated modes of interaction of PdNPs with DNA.

Table 2 The Sonogashira reaction of aryl iodides and aryl acetylenes catalysed by PdNPs/DNA.^a

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Aryl iodide	Aryl acetylene	Product	Conversion (%) ^b	Yield (%) ^c
			>99	85
			83	78
			89	81
			78	69
			88	83
			78	70
			85 ^d (95) ^e	80 ^e
			82 ^d (87) ^e	77 ^e
			70	62
			84	63
			62	54

^a Aryl iodide (**1**, 1.0 mmol), aryl acetylene (**2**, 1.0 mmol), PdNPs/DNA (8 mg, 0.5 mol%) and Cs₂CO₃ (1.4 mmol) in MeOH (2 mL) at 65 °C in air, 24 h. ^b Conversion determined by GLC using *n*-decane as the internal standard referred to **1**. ^c Isolated yield after column chromatography. ^d PdNPs/DNA (16 mg, 1.0 mol%). ^e Reaction at 80 °C.

Bases other than Cs_2CO_3 , either inorganic or organic, proved to exert a detrimental effect on the conversion, being in all cases below 30% (Table 1, entries 13–17). One control experiment in the absence of the base failed and confirmed the necessity for an external base in order to the reaction to occur (Table 1, entry 18).

We next studied the effect of the palladium loading and the reaction time. Either lower or higher Pd loadings than 0.5 mol% did not increase the conversion (Table 1, entries 19–21), whereas prolonged stirring for 24 h is recommended to attain the highest conversion (Table 1, compare entry 10 with entries 22–25). In view of the above results, the catalytic system of choice consists of 0.5 mol% Pd/DNA and Cs_2CO_3 in MeOH at 65 °C for 24 h in air (Table 1, entry 10).

Substrate scope in the Sonogashira coupling reaction

The optimised catalytic system and reaction conditions were applied to a series of aryl iodides and aryl acetylenes (Table 2). Besides simple iodoaromatics, such as iodobenzene (**1a**) and 1-iodonaphthalene (**1b**), those *para*-substituted with electron-withdrawing groups (**1c** and **1d**) also gave good conversions and isolated yields of the Sonogashira products. Iodobenzenes substituted with electron-donating substituents (**1e** and **1f**) at the *para* position reacted sluggishly under the standard reaction conditions; this apparent limitation could be overcome by either increasing the amount of catalyst (1.0 mol% Pd) or the reaction temperature (80 °C). In contrast, diiodobenzenes (**1g** and **1h**) reacted nicely with phenylacetylene (**2a**) to produce the conjugated triaryl diynes **3ga** and **3ha** in good conversions and moderate isolated yields. Particularly interesting is the result of **3ha**, which must proceed through a more sterically encumbered 1-iodo-2-(phenylethynyl)benzene intermediate. The reaction conditions were compatible with the presence of an acidic hydrogen, such as that in 1-(4-hydroxy-3-iodophenyl)ethanone (**1i**), which furnished the trisubstituted phenol **3ia** in moderate yield.

Not only aromatic but aliphatic alkynes could be coupled with iodobenzene under the standard conditions to provide a range of alkyl aryl acetylenes (Table 3). Linear-alkyl acetylene **2d** reacted quantitatively, in contrast with the cyclic alkyl counterpart **2e**. The controlled mono-arylation of the terminal diyne **2f** leaves open the possibility for a second arylation reaction. Furthermore, the catalytic system was compatible with the use of functionalised alkynes (**2g–2i**), even bearing acidic hydroxyl groups, to form the expected products in good isolated yields.

Catalyst recycling

We next explored the recycling capability of PdNPs/DNA in the coupling of iodobenzene (**1a**) with phenylacetylene (**2a**) to give **3aa**. In order to check the performance after each cycle, the catalyst was removed from the reaction medium by centrifugation (Figure 10); the resulting precipitate was washed, dried and used in subsequent cycles under the standard conditions without any further treatment. As depicted in Figure 11, the activity of the catalyst (only 8 mg) could be extended over five cycles with no apparent loss in the

Table 3 The Sonogashira reaction of iodobenzene and aliphatic alkynes catalysed by PdNPs/DNA.^a DOI: 10.1039/C7CY00001D

Starting alkyne	Product	Conv. (%) ^b	Yield (%) ^c
		>99	73
		75	68
		>99	71
		>99	86
		90	84
		73	71

^a Iodobenzene (**1a**, 1.0 mmol), alkyne (**2**, 1.0 mmol), PdNPs/DNA (8 mg, 0.5 mol%) and Cs_2CO_3 (1.4 mmol) in MeOH at 65 °C in air, 24 h. ^b Conversion determined by GLC using *n*-decane as the internal standard referred to **1a**. ^c Isolated yield after column chromatography.

first four and some decrease in the fifth run.

The leaching issue was assessed by filtering a reaction after the first run and analysing a sample of the filtrate by ICP-MS. The palladium content in solution was determined to be 0.01 wt% of the original amount. The hot filtration test was applied to a 33% (**3aa**) conversion reaction (2 h); further heating of the filtrate at 65 °C for 24 h gave **3aa** in a lower percentage (11%) due to by-product formation. Therefore, according to this minor inactive leaching it can be concluded that the interaction of DNA with the palladium nanoparticles leads to a quite robust heterogeneous catalyst endowed of good recycling properties.



Fig. 10 Pictures showing the reaction mixture before (left) and after (right) centrifugation.

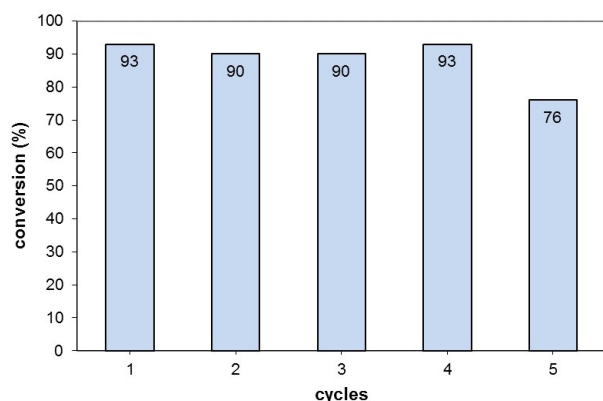


Fig. 11 Recycling of PdNPs/DNA in the synthesis of **3aa**.

Comparison with commercial and other Pd catalysts

Ideally, any laboratory-made metal catalyst should manifest distinguished catalytic activity when compared with the commercial counterparts. This different behaviour could justify the time and resources utilised in the preparation of the former. With this hypothesis in mind, a variety of commercial palladium catalysts, including three homogeneous and one heterogeneous were tested in the coupling reaction of iodobenzene (**1a**) and phenylacetylene (**2a**) (Table 4). The best results were recorded with PdNPs/DNA as catalyst in both terms of conversion and purity (Table 4, entry 1). As illustrated in Figure 12, the commercial catalysts led to the formation of abundant by-products under the standard conditions, whereas the reaction with PdNPs/DNA was very clean.

Table 4 Comparison of PdNPs/DNA with commercial palladium catalysts.^a

$\text{PhI} + \text{Ph}-\text{C}\equiv\text{CH} \xrightarrow[\text{Cs}_2\text{CO}_3, \text{MeOH}, 65^\circ\text{C}, 24\text{ h}]{\text{catalyst (0.5 mol\%)}} \text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$				
1a	2a			3aa
Entry	Catalyst	TLC label	Conversion (%) ^b	
1	PdNPs/DNA	A	>99	
2	PdCl ₂	B	48	
3	Pd(OAc) ₂	C	51	
4	PdCl ₂ (PPh ₃) ₂	D	49	
5	Pd/C (10 wt%)	-	42 ^c	

^a Iodobenzene (**1a**, 0.5 mmol), alkyne (**2a**, 0.5 mmol), catalyst (0.5 mol%) and Cs₂CO₃ (0.7 mmol) in MeOH at 65 °C in air, 24 h. ^b Conversion determined by GC-MS. ^c Alkyne homocoupling product **4a** was formed in 51%.

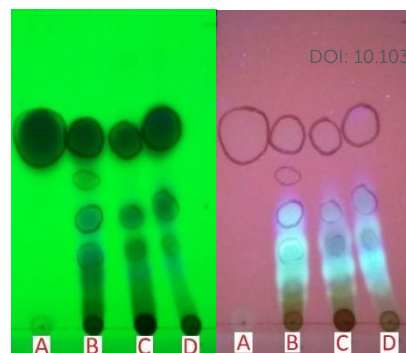


Fig. 12 TLC plate images under the UV lamp irradiation of 254 nm (left) and 365 nm (right) corresponding to the crudes of the reactions shown in Table 4 (entries 1–4).

Certainly, commercial Pd(OAc)₂ and PdCl₂(PPh₃)₂ have been successfully applied to the Sonogashira reaction in other optimised copper-free catalytic systems.²⁸ However, the use of an inert atmosphere is mandatory in most cases and the catalyst reutilisation is hampered because of their homogeneous nature. Pd/C makes the possibility of reutilisation plausible and, even though broadly used in combination with CuI and PPh₃,^{10d,29} some copper- and phosphine-free procedures have been described in the presence of an inert atmosphere.³⁰

Mechanistic aspects

The mechanism of the copper-free palladium-catalysed Sonogashira reaction has been a topic of continuous and intense debate.^{10i,31} While most of these studies have been focused on the homogeneous version of the reaction, the heterogeneous counterpart has been disregarded and less understood. In our case, we were intrigued about the role of the different Pd species and DNA; various control experiments were conducted with this purpose.

The ease of ionisation of the alkyne C_{sp}-H bond can be measured by H/D exchange and may give an idea about the metal species participating in its activation. Two alkynes of notable different pK_a, phenylacetylene (**2a**) and 1-octyne (**2d**), were subjected to the deuteration experiments in order to get more reliable information (Table 5). As expected, phenylacetylene (**2a**) got much easier ionised than 1-octyne (**2d**), with near quantitative deuteration of the former irrespective of the presence of DNA, PdNPs/DNA or commercial PdO·H₂O (Table 5, entries 2–4). It is noteworthy that DNA promoted the H/D exchange of phenylacetylene (**2a**) (Table 5, compare entries 1 and 2) but not at all that of 1-octyne (**2d**) (Table 5, compare entries 2 and 6). On the contrary, PdNPs/DNA and PdO·H₂O were both effective on phenylacetylene (**2a**) and 1-octyne (**2d**), though to a lesser extent on the latter (Table 5, compare entries 3 and 4 with 7 and 8). These results suggest that the PdO contained in PdNPs/DNA could enhance the acidity of the alkyne C_{sp}-H bond facilitating its deprotonation.³²

We next paid attention to the evolution of the palladium species in the reaction medium under the standard conditions on the basis of XPS analysis. First, PdNPs/DNA in MeOH was warmed at 65 °C during 24 h; a substantial amount of Pd(0)

Table 5 Alkyne C_{sp}-H ionisation.^a

$\text{R}-\text{C}\equiv\text{CH} \xrightarrow[65\text{ }^{\circ}\text{C}, 24\text{ h}]{\text{catalyst, CD}_3\text{OD}} \text{R}-\text{C}\equiv\text{CD} \quad \text{D}_1\text{-}\mathbf{2}$			
Entry	Alkyne	Catalyst ^b	D ₁ - 2 (%) ^c
1	PhC≡CH (2a)	-	12
2	PhC≡CH (2a)	DNA ^d	97
3	PhC≡CH (2a)	PdNPs/DNA	96
4	PhC≡CH (2a)	PdO·H ₂ O	99
5	<i>n</i> -C ₆ H ₁₃ C≡CH (2d)	-	0
6	<i>n</i> -C ₆ H ₁₃ C≡CH (2d)	DNA ^d	0
7	<i>n</i> -C ₆ H ₁₃ C≡CH (2d)	PdNPs/DNA	74
8	<i>n</i> -C ₆ H ₁₃ C≡CH (2d)	PdO·H ₂ O	73

^a Alkyne (**2**, 1.0 mmol) and catalyst in CD₃OD at 65 °C in air, 24 h. ^b 0.5 mol% Pd; ^c Deuteration percentage determined by GC-MS. ^d 8 mg of DNA.

was generated at the expense of all the PdO and, might be, of some PdO₂ (Figure 13a). When commercial PdO·H₂O was submitted to the same essay, approximately, half of it was transformed into Pd(0) (Figure 13b); this partial reduction could be related to the bulk character of the PdO compared to the nanosized PdO in PdNPs/DNA. We also analysed the recovered PdNPs/DNA after a successful standard reaction of iodobenzene (**1a**) and phenylacetylene (**2a**) (Figure 13c); Pd(0) was the major species followed by PdO₂, whereas the presence of PdO was imperceptible by this technique and negligible in any case. Opposite to this was the outcome for a failed reaction of 4-iodoaniline (**1f**) and phenylacetylene (**2a**) under the standard conditions, where a minute amount of Pd(0) was formed (Figure 13d). Consequently, there is an evident trend to accumulate Pd(0) from a working catalytic cycle which must involve Pd(0)/Pd(II) rather than the Pd(II)/Pd(IV) system. Considering the original PdO/PdO₂ ratio in PdNPs/DNA (Figure 7) and the Pd(0)/PdO₂ ratio in Figures 13a and 13c, it seems reasonable to propose that part of the PdO₂ is also converted into Pd(0).

Given the complexity of DNA, we tried to additionally ascertain the function of its different components within the catalytic system. Thymine and guanine were selected as examples of the pyrimidine and purine DNA bases, respectively, together with diammonium hydrogenphosphate and ammonium dihydrogenphosphate as the equivalent DNA phosphate units. The influence of these additives in the reaction of iodobenzene (**1a**) and phenylacetylene (**2a**) catalysed by PdNPs/DNA is presented in Table 6. The addition of thymine markedly depleted the catalytic activity but guanine inhibited the reaction (Table 6, entries 2 and 3, respectively). This behaviour could be understood as the bases in DNA having a stabilising effect on the PdNPs; it is known that stabilisers can impede the increase of the nanoparticle size but an excess of them can make the catalyst less active or inactive.¹⁰ⁱ The stronger impact of guanine could be connected with the presence of the imino N atoms in its structure and the known affinity of the latter for PdNPs,²⁵ as also noted by XPS (see above). Conversely, the phosphates did not essentially interfere in the reaction (Table 6, entries 4 and 5), reinforcing the major role of the bases in the catalytic activity.

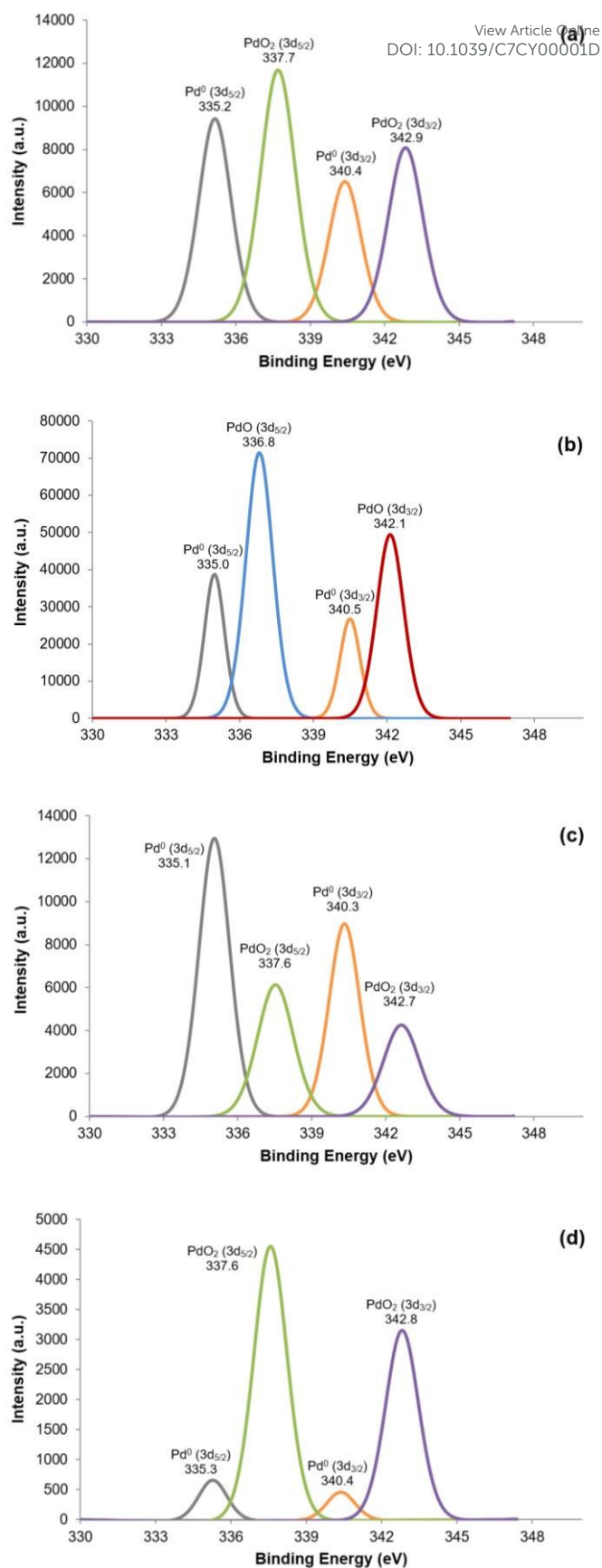


Fig. 13 XPS spectra of (a) PdNPs/DNA, MeOH, 65 °C, 24 h; (b) PdO·H₂O, MeOH, 65 °C, 24 h; (c) recovered catalyst after a successful reaction of (**1a**) and (**2a**), (d) recovered catalyst after a failed reaction of (**1f**) and (**2a**).

Table 6 The effect of different additives on the reaction of **1a** and **2a**.^a

Entry	Catalyst ^b	Additive ^c	3aa (%) ^d
1	PdNPs/DNA	-	>99
2	PdNPs/DNA	thymine	12
3	PdNPs/DNA	guanine	0
4	PdNPs/DNA	(NH ₄) ₂ HPO ₄	90
5	PdNPs/DNA	(NH ₄)H ₂ PO ₄	88
6	PdO·H ₂ O	-	2
7	PdO·H ₂ O	DNA	0
8	PdO·H ₂ O	thymine	0
9	PdO·H ₂ O	guanine	0

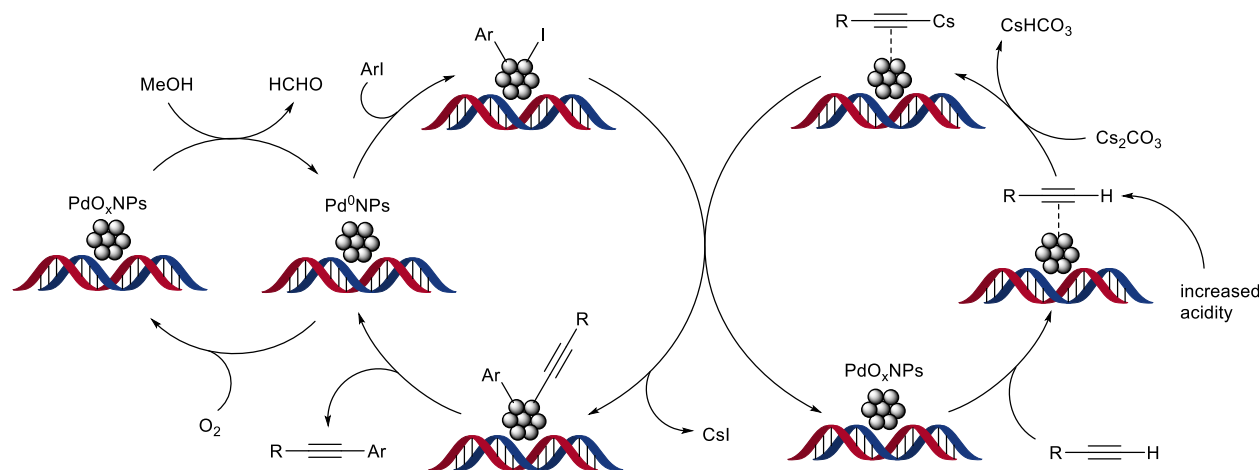
^a Iodobenzene (**1**, 1.0 mmol), phenylacetylene (**2**, 1.0 mmol), catalyst (0.5 mol%) and Cs₂CO₃ (1.4 mmol) in MeOH (2 mL) at 65 °C in air, 24 h. ^b 0.5 mol% Pd; ^c 10 mg. ^d Conversion determined by GLC.

Finally, the activity of commercial PdO·H₂O was compared with that of PdNPs/DNA. In spite of the fact that Pd(0) was formed

from PdO·H₂O (Figure 13b), its catalytic activity was virtually nil irrespective of the absence or presence of additives (Table 6, entries 6–9). Seemingly, the nanosized nature of the DNA-stabilised PdNPs makes all the difference when compared with the bulk Pd of the commercial catalyst.

Three types of mechanisms are generally considered in C-C coupling reactions catalysed by PdNPs:¹⁰ⁱ (a) PdNPs acting as an authentic heterogeneous catalyst through its surface; (b) leaching of Pd(0) atoms from the PdNPs which get into a homogeneous catalytic cycle; (c) oxidative addition taking place on the PdNPs surface with subsequent leaching of PdArX species which start a homogeneous catalytic cycle.

The aforementioned negative filtration test lays aside the mechanistic option (b). In this sense, further useful information was obtained from two poisoning tests:³³ the addition of either mercury (10 equiv.) or CS₂ (0.25 equiv.) inhibited the standard reaction between iodobenzene (**1a**) and phenylacetylene (**2a**), what highly evidences a heterogeneous catalysis on the nanoparticle surface.

**Fig. 14** Reaction mechanism proposed for the Sonogashira coupling of aryl iodides and alkynes catalysed by PdNPs/DNA.

Concluding this section, a reaction mechanism was put forward on the basis of all the above experimentation (Figure 14). On one hand, the catalytically active Pd(0) species could be produced by the reduction of PdO (mainly)³⁴ and PdO₂ by the action of MeOH which, in turn, would get oxidised to formaldehyde. This becomes clear when one examines the XPS of PdNPs/DNA after its preparation in MeOH at room temperature [exempt from Pd(0), Figure 7] and the XPS of PdNPs/DNA after warming in MeOH [presence of Pd(0), Figure 13a]. On the other hand, both PdO and PdO₂ could participate in the alkyne activation, surely, with a more important contribution of the latter given the low levels of PdO noted after the reaction (Figure 13c); it is normally accepted that alkyne activation occurs by the coordination of RPD_x species to the C≡C bond but, from Table 5, it is obvious that other components in the reaction medium can exert the same effect. Alkyne deprotonation by the base would give the

corresponding caesium acetylide;³⁵ iodide displacement by the latter from the oxidative addition species (ArPdI), with the concomitant formation of the arylpalladium acetylide, followed by reductive elimination would afford the product with regeneration of Pd(0).

Conclusions

We have demonstrated that DNA is a convenient support for palladium nanoparticles, giving rise to a catalyst which is applicable to the copper- and ligand-free Sonogashira-Hagihara reaction. A series of aryl iodides bearing electronically different functional groups, as well as diiodides, have been successfully coupled with either aromatic or aliphatic alkynes to give the expected products in moderate-to-high isolated yields (51–86%). In our opinion, the following advantages can be remarked on this catalytic system: (a)

simple preparation of the catalyst at ambient temperature involving a biodegradable support; (b) coupling under relatively mild conditions (65 °C), what can prevent a shrinkage of the catalytic activity by the Ostwald ripening process; (c) the absence of copper salts and ligands; (d) relatively low metal loading (0.5 mol% Pd) and low leaching, (e) use of an easy-to-remove recommended solvent (MeOH),¹¹ (f) all the experiments are carried out in air, (g) alkyne homocoupling is minimised, (h) the catalyst can be easily recovered and reused in five cycles (93–76% conversion) and (i) it is superior to some commercial homogeneous and heterogeneous palladium catalysts. A thorough mechanistic survey comprising the major part played by the different constituents of the catalyst has been provided, bolstering the heterogeneous nature of the process.

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Experimental

Typical procedure for the preparation of PdNPs/DNA. A solution of Li_2PdCl_4 (0.50 M, 0.15 mL) in MeOH (1 mL) and NaOAc (0.05 g) were added to 0.10 g of salmon-sperm DNA at room temperature under argon. Stirring was continued for 2–3 days and, then, the mixture was diluted with H_2O (2 mL). The resulting precipitate was filtered and washed with H_2O (3×2 mL) to produce a grey solid which was dried at room temperature.

Typical procedure for the cross-coupling of aryl iodides with alkynes catalysed by PdNPs/DNA. All reactions were performed using tubes in a multi-reactor system under air. Cs_2CO_3 (1.4 mmol, 456 mg) was slowly added to a solution of iodobenzene (**1a**, 1.0 mmol, 0.11 mL) and phenylacetylene (**2a**, 1.0 mmol, 0.10 mL) in MeOH (2 mL), followed by the addition of PdNPs/DNA (8 mg, 0.5 mol%) and additional MeOH (2 mL). The reaction mixture was subjected to constant stirring at 65 °C for 24 h, time after which it became yellowish cloudy as a result of the catalyst being converted into slurry. The solvent was evaporated under vacuum, followed by the addition of EtOAc (3×5 mL) and washing with water (3×5 mL). The organic phase was dried with anhydrous Mg_2SO_4 , filtered through Celite and the filtrate was evaporated under reduced pressure. The resulting brown amber reaction crude was purified by column chromatography (hexane) to give white crystals of 1,2-diphenylethyne (**3aa**) in 85% yield.

Notes and references

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Graphical abstract

Palladium nanoparticles on DNA have been shown to be an effective and reusable heterogeneous catalyst for the copper- and ligand-free Sonogashira coupling reaction of aryl iodides under mild conditions in air.

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